CLAIMS

What is claimed is:

1. A substantially purified polypeptide selected from the group consisting of:
   (a) a polypeptide comprising a sequence that is at least 80% identical to a sequence selected from the group consisting of SEQ ID NO:2, 4, 6, 8, 10, 12, 24, 31, 34, and 37-39, wherein the polypeptide binds to nectin-1; and
   (b) a fragment of (a) that binds to nectin-1.
2. The substantially purified polypeptide of claim 1, wherein the polypeptide is selected from the group consisting of:
   (a) a polypeptide comprising a sequence that is at least 90% identical to a sequence selected from the group consisting of SEQ ID NO:2, 4, 6, 8, 10, 12, 24, 31, 34, and 37-39, wherein the polypeptide binds to nectin-1; and
   (b) a fragment of (a) that binds to nectin-1.
3. The substantially purified polypeptide of claim 1, wherein the polypeptide is selected from the group consisting of:
   (a) a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:2, 4, 6, 8, 10, 12, 24, 31, 34, and 37-39; and
   (b) a fragment of (a) that binds to nectin-1.
4. A substantially purified soluble polypeptide selected from the group consisting of:
   (a) a polypeptide comprising a sequence that is at least 80% identical to the extracellular domain of SEQ ID NO:2, 4, 6, 8, 10, 12, 24, 31, 34, and 37-39, wherein the polypeptide binds to nectin-1;
   (b) a fragment of (a) that binds to nectin-1; and
   (c) a fragment of (a) that inhibits endothelial cell migration.
5. The substantially purified soluble polypeptide of claim 4, wherein the polypeptide is selected from the group consisting of:
   (a) a polypeptide comprising a sequence that is at least 90% identical to the extracellular domain of SEQ ID NO:2, 4, 6, 8, 10, 12, 24, 31, 34, 37-39, wherein the polypeptide binds to nectin-1;
   (b) a fragment of (a) that binds to nectin-1; and
   (c) a fragment of (a) that inhibits endothelial cell migration.
6. The substantially purified polypeptide of claim 4, wherein the polypeptide is selected from the group consisting of:
   (a) a polypeptide comprising a sequence selected from the group consisting of: from about x_1 to 404 of SEQ ID NO:4 or 6 wherein x_1 is an amino acid between 1 and 39, from about amino acid 58 to 152 of SEQ ID NO:4 or 6, from about amino acid 58 to 250 of SEQ ID NO:4 or 6, from about amino acid 58 to 342 of SEQ ID NO:4 or 6, from about amino acid 58 to 404 of SEQ ID NO:4 or 6, from about amino acid 74 to 152 of SEQ ID NO:4 or 6, from about amino acid 74 to 250 of SEQ ID NO:4 or 6, from about amino acid 74 to 342 of SEQ ID NO:4 or 6, from about amino acid 74 to 404 of SEQ ID NO:4 or 6, from about amino acid 189 to 250 of SEQ ID NO:4 or 6, from about amino acid 189 to 342 of SEQ ID NO:4 or 6, from about amino acid 189 to 404 of SEQ ID NO:4 or 6, from about amino acid 287 to 342 of SEQ ID NO:4 or 6, and from about amino acid 287 to 404 of SEQ ID NO:4 or 6;

(b) a polypeptide comprising a sequence selected from the group consisting of: from about x_1 to 365 of SEQ ID NO:10 or 12 wherein x_1 is an amino acid between 1 and 39, from about amino acid 58 to 152 of SEQ ID NO:10 or 12, from about amino acid 58 to 250 of SEQ ID NO:10 or 12, from about amino acid 58 to 342 of SEQ ID NO:10 or 12, from about amino acid 58 to 365 of SEQ ID NO:10 or 12, from about amino acid 74 to 152 of SEQ ID NO:10 or 12, from about amino acid 74 to 250 of SEQ ID NO:10 or 12, from about amino acid 74 to 342 of SEQ ID NO:10 or 12, from about amino acid 74 to 365 of SEQ ID NO:10 or 12, from about amino acid 189 to 250 of SEQ ID NO:10 or 12, from about amino acid 189 to 342 of SEQ ID NO:10 or 12, from about amino acid 189 to 365 of SEQ ID NO:10 or 12, from about amino acid 287 to 342 of SEQ ID NO:10 or 12, and from about amino acid 287 to 365 of SEQ ID NO:10 or 12;

(c) a polypeptide comprising a sequence selected from the group consisting of from about x_2 to 349 of SEQ ID NO:24 or 34 wherein x_2 is an amino acid between 1 and 16, from about amino acid 27 to 350 of SEQ ID NO:36, from about amino acid 44 to 362 of SEQ ID NO:37, from about amino acid 39 to 242 of SEQ ID NO:38, and from about amino acid 44 to 363 of SEQ ID NO:39;

(d) a fragment of (a), (b), or (c) that binds to nectin-1; and

(e) a fragment of (a), (b), or (c) that inhibits endothelial cell migration.

7. A soluble polypeptide according to claim 4, further comprising a leucine zipper polypeptide, an Fc polypeptide, or a peptide linker.

8. The soluble polypeptide according to claim 7, comprising a sequence Z_1-X-Z_2, wherein Z_1 and Z_2 are each individually a soluble polypeptide selected from the group consisting of:

(a) a polypeptide comprising a sequence selected from the group consisting of: from about x_1 to 404 of SEQ ID NO:4 or 6 wherein x_1 is an amino acid between 1 and 39, from about amino acid 58 to 152 of SEQ ID NO:4 or 6, from about amino acid 58 to 250 of SEQ ID NO:4 or 6, from about amino acid 58 to 342 of SEQ ID NO:4 or 6, from about amino acid 58 to 404 of SEQ ID NO:4 or 6, from about amino acid 74 to 152 of SEQ ID NO:4 or 6, from about amino acid 74 to 250 of SEQ ID NO:4 or 6, from about amino acid 74 to 342 of SEQ ID NO:4 or 6, from about amino acid 74 to 404 of SEQ ID NO:4 or 6, from about amino acid 189 to 250 of SEQ ID NO:4 or 6, from about amino acid 189 to 342 of SEQ ID NO:4 or 6, from about amino acid 189 to 404 of SEQ ID NO:4 or 6, from about amino acid 287 to 342 of SEQ ID NO:4 or 6, and from about amino acid 287 to 404 of SEQ ID NO:4 or 6;

(b) a polypeptide comprising a sequence selected from the group consisting of: from about x_1 to 365 of SEQ ID NO:10 or 12 wherein x_1 is an amino acid between 1 and 39, from about amino acid 58 to 152 of SEQ ID NO:10 or 12, from about amino acid 58 to 250 of SEQ ID NO:10 or 12, from about amino acid 58 to 342 of SEQ ID NO:10 or 12, from about amino acid 58 to 365 of SEQ ID NO:10 or 12, from about amino acid 74 to 152 of SEQ ID NO:10 or 12, from about amino acid 74 to 250 of SEQ ID NO:10 or 12, from about amino acid 74 to 342 of SEQ ID NO:10 or 12, from about amino acid 74 to 365 of SEQ ID NO:10 or 12, from about amino acid 189 to 250 of SEQ ID NO:10 or 12, from about amino acid 189 to 342 of SEQ ID NO:10 or 12, from about amino acid 189 to 365 of SEQ ID NO:10 or 12, from about amino acid 287 to 342 of SEQ ID NO:10 or 12, and from about amino acid 287 to 365 of SEQ ID NO:10 or 12;

(c) a polypeptide comprising a sequence selected from the group consisting of from about x_2 to 349 of SEQ ID NO:24 or 34 wherein x_2 is an amino acid between 1 and 16, from about amino acid 27 to 350 of SEQ ID NO:36, from about amino acid 44 to 362 of SEQ ID NO:37, from about amino acid 39 to 242 of SEQ ID NO:38, and from about amino acid 44 to 363 of SEQ ID NO:39;

(d) a fragment of (a), (b), or (c) that binds to nectin-1; and

(e) a fragment of (a), (b), or (c) that inhibits endothelial cell migration,

and X is a peptide linker.

9. The soluble polypeptide of claim 4, wherein the polypeptide comprises a sequence selected from the group consisting of SEQ ID NO:13, 14, 15, 16, and 36.

10. A composition comprising a polypeptide of claim 1 and a pharmaceutically acceptable carrier.

11. A composition comprising a polypeptide of claim 4 and a pharmaceutically acceptable carrier.

12. An isolated polynucleotide encoding a polypeptide of claim 1.

13. An isolated polynucleotide encoding a polypeptide of claim 4.

14. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising a sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 30, 32, 33, or 35;

(b) a polynucleotide comprising a sequence selected from the group consisting of: from about nucleotide x_1 to 1212 of SEQ ID NO:3 or 5 wherein x_1 is a nucleotide between 1 and 115, from about nucleotide 172 to 456 of SEQ ID NO:3 or 5, from about nucleotide 172 to 750 of SEQ ID NO:3 or 5, from about nucleotide 172 to 1026 of SEQ ID NO:3 or 5, from about nucleotide 172 to 1212 of SEQ ID NO:3 or 5, from about nucleotide 222 to 456 of SEQ ID NO:3 or 5, from about nucleotide 222 to 750 of SEQ ID NO:3 or 5, from about nucleotide 222 to 1026 of SEQ ID NO:3 or 5, from about nucleotide 222 to 1212 of SEQ ID NO:3 or 5, from about nucleotide 567 to 750 of SEQ ID NO:3 or 5, from about nucleotide 567 to 1026 of SEQ ID NO:3 or 5, from about nucleotide 567 to 1212 of SEQ ID NO:3 or 5, from about nucleotide 861 to 1026 of SEQ ID NO:3 or 5, and from about nucleotide 861 to 1212 of SEQ ID NO:3 or 5;

(c) a polynucleotide comprising a sequence selected from the group consisting of: from about nucleotide x_1 to 1098 of SEQ ID NO:9 or 11 wherein x_1 is a nucleotide between 1 and 115, from about nucleotide 172 to 456 of SEQ ID NO:9 or 11, from about nucleotide 172 to 750 of SEQ ID NO:9 or 11, from about nucleotide 172 to 1026 of SEQ ID NO:9 or 11, from about nucleotide 172 to 1098 of SEQ ID NO:9 or 11, from about nucleotide 222 to 456 of SEQ ID NO:9 or 11, from about nucleotide 222 to 750 of SEQ ID NO:9 or 11, from about nucleotide 222 to 1026 of SEQ ID NO:9 or 11, from about nucleotide 222 to 1098 of SEQ ID NO:9 or 11, from about nucleotide 567 to 750 of SEQ ID NO:9 or 11, from about nucleotide 567 to 1026 of SEQ ID NO:9 or 11, from about nucleotide 567 to 1098 of SEQ ID NO:9 or 11, from about nucleotide 861 to 1026 of SEQ ID NO:9 or 11, and from about nucleotide 861 to 1098 of SEQ ID NO:9 or 11;

(d) a polynucleotide comprising a sequence from about nucleotide 79 to 1047 of SEQ ID NO:32 or 33;

(e) a polynucleotide that hybridizes under moderate to highly stringent conditions to a polynucleotide comprising the sequence of (a), (b), (c), or (d) and encoding a polypeptide that binds to nectin-1;

(f) a nucleotide sequence complementary to a sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 30, 32, 33 or 35; and

(g) any of nucleotide sequences of (a) to (f) wherein T can also be U.

15. An isolated polynucleotide comprising a sequence of claim 14 operably linked to a polynucleotide encoding a polypeptide selected from the group consisting of an Fc polypeptide, a leucine zipper polypeptide, and a peptide linker.
16. An expression vector comprising a polynucleotide of claim 12.
17. A recombinant host cell genetically engineered to contain the polynucleotide of claim 12.
18. A method for producing a polypeptide, comprising culturing the host cell of claim 17 under conditions promoting expression of the polypeptide.
19. A polypeptide produced by culturing the host cell of claim 17 under conditions to promote expression of the polypeptide.
20. A substantially purified antibody that specifically binds to a polypeptide of claim 1.
21. The antibody of claim 20, wherein the antibody is a monoclonal antibody.
22. The antibody of claim 20, wherein the antibody is a human or a humanized antibody.
23. The antibody of claim 20, wherein the antibody blocks a biological activity of a nectin-3 or nectin-4 polypeptide.
24. A method of designing an inhibitor or binding agent of a polypeptide of claim 1, comprising determining the three-dimensional structure of the polypeptide, analyzing the three-dimensional structure for binding sites of substrates or ligands, designing a molecule that is predicted to interact with the polypeptide, and determining the inhibitory or binding activity of the molecule.
25. A method for identifying an agent that modulates an activity of a polypeptide of claim 1, comprising:
    (a) contacting the agent with the polypeptide under conditions such that the agent and polypeptide interact; and
    (b) determining an activity of the polypeptide in the presence of the agent compared to a control, wherein a change in activity is indicative of an agent that modulates the polypeptide's activity.
26. The method of claim 25, wherein the agent is selected from the group consisting of an antibody, a small molecule, a peptide, and a peptidomimetic.
27. The method of claim 25, wherein the activity is selected from the group consisting of nectin-1 binding activity, cell adhesion activity, adherens junction formation activity, epithelial or endothelial barrier function activity, endothelial-, epithelial-, or smooth muscle cell-proliferation or migration activity, and viral polypeptide binding activity.
28. A method of modulating an activity of a nectin-1 polypeptide, comprising contacting the nectin-1 polypeptide with a polypeptide of claim 1.
29. A method of identifying an agent that modulates binding between nectin-1 and a polypeptide of claim 1, comprising contacting a sample containing nectin-1 with the agent and measuring the interaction of nectin-1 with the polypeptide compared to a control sample, wherein a change in the binding between nectin-1 and the polypeptide compared to the control is indicative of an agent that modulates binding.
30. The method of claim 29, wherein the agent is selected from the group consisting of a polypeptide, a peptide, an antibody, a peptidomimetic, and a small molecule.
31. A method of modulating cellular proliferation or migration, comprising contacting a cell with an agent that modulates nectin-1 activity or expression under conditions such that the cell and the agent interact.
32. The method of claim 31, wherein the cell is selected from the group consisting of an endothelial cell, an epithelial cell, and a smooth muscle cell.
33. The method of claim 32, wherein the smooth muscle cell is a vascular smooth muscle cell.

34. The method of claim 31, wherein the agent is selected from the group consisting of a peptide, a polypeptide, a peptidomimetic, a polynucleotide, antibody, and a small molecule.
35. The method of claim 34, wherein the polypeptide is a soluble nectin-3 or nectin-4 polypeptide.
36. The method of claim 35, wherein the soluble polypeptide further comprises an Fc, leucine zipper or peptide linker polypeptide.
37. A method of inhibiting angiogenesis in a mammal in need of such treatment, comprising administering to the mammal an inhibition-effective amount of a polypeptide of claim 4.
38. The method of claim 37, wherein the polypeptide is selected from the consisting of:

(a) a polypeptide comprising a sequence selected from the group consisting of: from about x_1 to 404 of SEQ ID NO:4 or 6 wherein x_1 is an amino acid between 1 and 39, from about amino acid 58 to 152 of SEQ ID NO:4 or 6, from about amino acid 58 to 250 of SEQ ID NO:4 or 6, from about amino acid 58 to 342 of SEQ ID NO:4 or 6, from about amino acid 58 to 404 of SEQ ID NO:4 or 6, from about amino acid 74 to 152 of SEQ ID NO:4 or 6, from about amino acid 74 to 250 of SEQ ID NO:4 or 6, from about amino acid 74 to 342 of SEQ ID NO:4 or 6, from about amino acid 74 to 404 of SEQ ID NO:4 or 6, from about amino acid 189 to 250 of SEQ ID NO:4 or 6, from about amino acid 189 to 342 of SEQ ID NO:4 or 6, from about amino acid 189 to 404 of SEQ ID NO:4 or 6, from about amino acid 287 to 342 of SEQ ID NO:4 or 6, and from about amino acid 287 to 404 of SEQ ID NO:4 or 6;

(b) a polypeptide comprising a sequence selected from the group consisting of: from about x_1 to 365 of SEQ ID NO:10 or 12 wherein x_1 is an amino acid between 1 and 39, from about amino acid 58 to 152 of SEQ ID NO:10 or 12, from about amino acid 58 to 250 of SEQ ID NO:10 or 12, from about amino acid 58 to 342 of SEQ ID NO:10 or 12, from about amino acid 58 to 365 of SEQ ID NO:10 or 12, from about amino acid 74 to 152 of SEQ ID NO:10 or 12, from about amino acid 74 to 250 of SEQ ID NO:10 or 12, from about amino acid 74 to 342 of SEQ ID NO:10 or 12, from about amino acid 74 to 365 of SEQ ID NO:10 or 12, from about amino acid 189 to 250 of SEQ ID NO:10 or 12, from about amino acid 189 to 342 of SEQ ID NO:10 or 12, from about amino acid 189 to 365 of SEQ ID NO:10 or 12, from about amino acid 287 to 342 of SEQ ID NO:10 or 12, and from about amino acid 287 to 365 of SEQ ID NO:10 or 12;

(c) a polypeptide comprising a sequence selected from the group consisting of from about x_2 to 349 of SEQ ID NO:24 or 34 wherein x_2 is an amino acid between 1 and 16, from about amino acid 27 to 350 of SEQ ID NO:36, from about amino acid 44 to 362 of SEQ ID NO:37, from about amino acid 39 to 242 of SEQ ID NO:38, and from about amino acid 44 to 363 of SEQ ID NO:39;and

(d) a fragment of (a), (b), or (c) that binds to nectin-1.

39. A method for treating an endothelial proliferation, migration, or angiogenic condition comprising contacting a a tissue or a subject in need of such treatment with a polypeptide of claim 4.
40. The method of claim 39, wherein the endothelial proliferation, migration, or angiogenic condition is selected from the group consisting of ischemia, athlerosclerosis, ischemia-reperfusion injury, stroke, thrombosis, restenosis, and tumor growth.
41. The method of claim 39, wherein the polypeptide comprises a sequence as set forth in SEQ ID NO:13, 14, 15, 16, or 36.
42. The method of claim 39, wherein the contacting is *in vitro*.

43. The method of claim 39, wherein the contacting is *in vivo*.
44. A method for treating a viral infection comprising administering a polypeptide of claim 4 to a subject.
45. The method of claim 44, wherein the viral infection is a herpesvirus infection.
46. A method for increasing adherens junction formation activity, epithelial or endothelial barrier function activity, or cell adhesion activity comprising contacting a cell with at least one polypeptide of claim 1.
47. A method for decreasing cell adhesion activity, adherens junction formation activity, epithelial or endothelial barrier function activity, endothelial-, epithelial-, or smooth muscle cell-proliferation or migration activity, or viral polypeptide binding activity comprising contacting a cell with at least one polypeptide of claim 1.
48. A method for treating a disease or disorder associated with cell adhesion activity, adherens junction formation activity, epithelial or endothelial barrier function activity, endothelial proliferation or migration activity, viral polypeptide binding activity, or angiogenesis in a subject comprising administering a polypeptide of claim 1 or an antibody thereto to the subject.
49. The method of claim 48, wherein the epithelial or endothelial barrier function disorder is selected from the group consisting of inflammation, sepsis, edema, diabetic retinopathy, asthma, allergy, allograft rejection, metastasis of cancer cells, paracellular transport disorders such as magnesium transport defects in the kidney, and inflammatory bowel disease.
50. The method of claim 37, wherein the polypeptide comprises a sequence selected from the group consisting of SEQ ID NO:13, 14, 15, 16, and 36.
51. The method of of claim 37, wherein the polypeptide is in the form of a multimer.
52. The method of claim 51, wherein the multimer is a dimer or trimer.
53. The method of claim 51, wherein the multimer comprises an Fc polypeptide, a leucine zipper, or a peptide linker.